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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER

ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/507,968	Yu et al.	
	Examiner	Art Unit	
	Sarada C Prasad	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-359* is/are pending in the application.

4a) Of the above claim(s) *1-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-359* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10*.
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other

Detailed Action

1. Applicant's election with traverse of Group II (claims 17-18, 20, 22) in Paper No. 9 (8/14/01) is acknowledged. Amendment A of Paper No. 9 (8/14/01) has been entered with the effect that original claims 17, 18, 20, and 22 have been cancelled, new claims 26-359 have been added (Paper No. 9, page 49, 2nd para, lines 1-2), and amendments to specification have been entered. Currently, claims 1-16, 19, 21, 23-25 and 26-359 are pending.

The traversal is on the ground(s) that a search of the polynucleotide claims would clearly provide useful information for the polypeptide claims and a search of the polypeptide claims, as a matter of routine, would include a search for antibodies and hence restriction of original claims 1-25 to Groups I, II, III is not proper. This is not found persuasive because the inventions of Groups I, II and III, directed to polynucleotide, polypeptide, and antibodies are distinct as noted in the last Office Action, as shown by the distinctness described therein. Applicant's attention is directed to MPEP 806.05. Contrary to Applicants' assertion that any search of the prior art in regard to Group I would reveal whether any prior art exists as to the other inventions of Groups II and III, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter. Furthermore, divergent classification of the three Groups of inventions I-III has been an additional criterion for the restriction of the claims 1-26 into three distinct inventions. Each of these inventions would require non-cohesive classification searches posing an undue burden for the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Currently, original claims 1-16, 19, 21, 23-25 have been withdrawn from consideration as being non-elected, and new claims 26-359 are under consideration.

Specification

2a. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. For example: sequences without corresponding SEQ ID NOs. (page 342; para 3, lines 6-8; page 343, para 5, lines 5-6).

Claim Rejections - 35 USC § 112-First paragraph-Scope of enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 26-359 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for only an isolated protein comprising full length polypeptide of SEQ ID NO. 2 of 1-285 amino acids, that can enhance lymphocyte proliferation, and an isolated polypeptide consisting of amino acid sequence of 134-285 of SEQ ID No. 2, does not reasonably provide enablement for

(i) an isolated protein comprising an amino acid sequence consisting of residues 1-46, or 47-72, or 73-285 of SEQ ID No. 2; or an isolated protein that is 90 or 95% identical to residues 1-46, or 47-72, or 73-285 of SEQ ID No. 2;

(ii) an isolated protein comprising a first amino acid sequence that is 90% or more identical to a second amino acid of either 1-285 of SEQ ID No.2 or 1-46 of SEQ ID NO. 2, or 47-72 of SEQ ID No.2, or 73-285 of SEQ ID No. 2;

(iii) an isolated protein comprising an amino acid sequence consisting of amino acid residues n to 285 of SEQ ID No. 2, where n is an integer in the range of 2-190, or 1-m of SEQ ID No. 2 where m is an integer in the range of 274-284; or n-m of SEQ ID No. 2 where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

(iv) an isolated protein comprising a first amino acid sequence that is 95% or more identical to a second amino acid sequence of either residues n-285 of SEQ ID No.2 where n is an integer in the range of 2-190, or residues 1-m of SEQ ID NO.2 where m is an integer in the range of 274-284, or residues n-m of SEQ ID NO. 2, wherein n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

(v) an isolated protein that is 90% or more identical to a sequence consisting of or comprising 134-285 of SEQ ID No.2 wherein said protein specifically binds an antibody that binds the protein of SEQ ID NO. 2;

(vi) an isolated protein comprising a fragment of the polypeptide of SEQ ID No.2, or 213) an isolated protein comprising an amino acid that is at least 9 contiguous amino acid residues of SEQ ID No. 2 wherein the protein specifically binds an antibody that specifically binds the polypeptide of SEQ ID No.2;

(vii) an isolated protein which comprises and amino acid sequence selected from residues 115-147, or 150-163, or 171-194, or 223-247, or 271-278 of SEQ ID No. 2 wherein the protein specifically binds to an antibody that specifically binds the polypeptide of SEQ ID No. 2; an amino terminal deletion protein mutant of the full length protein encoded by the cDNA of ATCC deposit no. 97768 .....; or a carboxy terminal deletion mutant of the full length protein encoded by the DNA contained in ATCC deposit No. 97768; or an amino and carboxy terminal deletion mutant of the full length protein encoded by the cDNA clone contained in the ATCC deposit No. 97768';

(vii) an isolated protein comprising a first amino acid sequence that is 95% identical to a second amino acid sequence selected from either full length or the c-terminal deletion mutant or the N-terminal deletion mutant of SEQ ID No. 2;

(viii) an isolated protein comprising a fragment of the polypeptide encoded by the cDNA clone wherein the fragment modulates leukocyte proliferation and differentiation or at least an isolated protein that specifically binds an antibody that specifically binds to SEQ ID No. 2.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification sets forth a polynucleotide of SEQ ID No.1 encoding a polypeptide of SEQ ID No.2 representing neutrokine-α (page 20 of specification Fig. 1A and 1B). The disclosure also provides details of the predicted intracellular, transmembrane, and the extracellular domains. Figure 3 also shows likely antigenic regions to be deduced by Jameson-

Wolf Plot proposing the regions of 115-147, 150-163, 1671-194, 223-246, 271-278 of SEQ ID No.2 (page 21).

The recitation of claims 26, 39,57,78, 103, 124, 142, 160, 178, 196, 213, 232, 247, 268, 290, 307, 324, 341 encompassing the above recited variants, fragments, polypeptides, antigenic peptides, fusion proteins, and the intended activities of the anticipated polypeptide fragments of SEQ ID NO. 2 is overly broad. The disclosure fails to provide any guidance by way of example for any one of the variant polypeptides claimed. The specification provides no details or guidance for the variation in the particular polypeptide encoded by SEQ ID No.1 or the generated variants of SEQ ID No.2, envisioned as recited in all of the independent claims. Such claim language can be interpreted to mean that the encoded polypeptides can include fragments of various lengths with sequence identical to or 90% or 95 % identical to SEQ ID No. 2. The specification lacks sufficient details and guidance to prepare sequence variants with function envisioned as being characteristic of the different regions of the polypeptide of instant SEQ ID No.2. It is not feasible for one of skill in the art to generate variants that have features of neutrokine-α without guidance as to which residues have been altered and found to be dispensable or not dispensable. It is essential to have guidance by way of example or by way of description of methods that have been employed to achieve variants, fragment or derivatives, fusion peptides of SEQ ID No.2 with any certainty. Even though the current state of the art would permit one of skill in the art to make several of these claimed peptides of SEQ ID NO.2, the applicant has not really made them or shown them to be employed in any assays as agonists or antagonists or competitors. The examples provided show gene therapy (page 333, using

endogenous neutrokine-alpha gene). Details of which portion of the molecule of neutrokine-α has been used are not obvious from the details provided.

The epitopic regions are determined based on prediction. The epitopic specificity of any of these fragments has not been shown to be true as in real examples nor any of these regions shown to be really antigenic determinants for any of the antibodies already made. What are the fusion proteins meant for and have they been put to use as envisioned for identification of a binding partner of the first or second protein. Have any of the N-terminal and C-terminal deletion mutants with 'n' and 'm' as amino acid delimiters been made and put to test for their usefulness.

It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic

anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Given the breadth of claims reciting fragments, derivatives, fusion peptides, variant polypeptides, fusion proteins of the variant polypeptides, antigenic peptides, in light of the predictability of the art that random arbitrary sequence changes do not ensure variants with features of SEQ ID No.2, as determined by the lack of working examples showing that the envisioned fragments of the protein do have specific utility, state of the art suggesting how guidance is needed for a skilled artisan even for single amino acid changes, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 27-38, 40-56, 58-77, 79-102, 104-123, 125-141, 143-159, 161-177, 179-195, 197-212, 214-231, 233-246, 248-267, 269-289, 291-301, 303-323, 325-340, 342-359 are rejected insofar as they depend on claims 26, 39, 57, 78, 103, 124, 142, 160, 178, 196, 213, 232, 247, 268, 290, 302, 324, 341.

Claim Rejections - 35 USC § 112-First paragraph-written description

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4a. Claims 26-359 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant written description sets forth a polypeptide of SEQ ID No. 2 representing neutrokine-α a member of the TNF superfamily (pages 21-22). However, the written description is not commensurate with 'variants, derivatives, fragments, fusion peptides of the variants with biological activities characteristic of neutrokine -α represented by an isolated polypeptide of SEQ ID No. 2'.

Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the claimed invention. Therefore, the Applicant is not in possession of the invention as claimed, at the time of filing. This is insufficient to support the claims as provided by the Revised Written description Guidelines published in the Federal register, vol 66, No.4, pages 1099-1111, Friday January 2001.

Instant specification provides general principles for making the polypeptide variants of SEQ ID No. 2 (pages 31-231). However, the disclosure fails to provide detailed description directed to the intended variants of the polypeptide of SEQ ID No.2 exhibiting TNF ligand like proteins with membrane association and function. It is not sufficient to name the claimed variant nucleic acids that can encode for polypeptides comprising 90 or 95% identity to SEQ ID No. 2, or the variant polypeptides without actually generating any of the said variants, and demonstrating their proper membership in the claimed genus.

Additionally, none of the proposed 'sequence variants' have been shown to be successfully achieved by the claimed nucleotide changes to SEQ ID No. 2 and yet have any of the features/properties and biological activity characteristic of the intended putative neutrokine-α

like protein. Since the disclosure fails to describe successful generation of any such variants with expected criteria, or describe what are the many permitted amino acid changes while preparing variants of SEQ ID No. 2, it can be reasonably concluded that Applicant is not in possession of the claimed variants at the time of filing.

Furthermore, the disclosure fails to describe the common attributes or characteristics that identify members of the genus, or an identified species with established structure and function. The genus is highly variant and the disclosure of a specific polypeptide sequence is insufficient to describe the genus consisting of variants of SEQ ID No.2. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species or a structural/functional feature sufficient to describe and enable the genus as broadly claimed.

Claims 27-38, 40-56, 58-77, 79-102, 104-123, 125-141, 143-159, 161-177, 179-195, 197-212, 214-231, 233-246, 248-267, 269-289, 291-301, 303-323, 325-340, 342-359 are rejected insofar as they depend on claims 26, 39, 57, 78, 103, 124, 142, 160, 178, 196, 213, 232, 247, 268, 290, 302, 324, 341.

4b. Claims 247-359 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 247, 268, 290, 302, 324, 341 recite the use of cDNA contained in ATCC Deposit No. 97668. This deposit is essential to the claimed invention. The reproduction of cDNA that encodes the neutrokine-α polypeptide must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public.

> If the deposits have been made under the terms of the Budapest treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating
>
> (a) that the ATCC deposit has been deposited under the Budapest treaty; and
> (b) that it will be irrevocably and without restriction or condition be released to the public upon issuance of a patent

would satisfy the deposit requirement made herein. See 37 CFR 1.808.

Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit, or 5 years after the last request for a sample, or for the enforceable life of a patent whichever is longer. See 37 CFR 1.806. If the deposit has not been made under the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have not been met.

Amendment of the specification to disclose the date of deposit and the complete name and the address of the depository is required.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the deposits described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a claim of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicants' possession at the time the application was filed. Applicants attention is directed to In re Lunduk, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985), and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Claims 248-267, 269-289, 291-301, 303-323, 325-340, 342-359 are rejected insofar as they depend on claims 247, 268, 290, 302, 324, 341.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 26-359 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,297,367 (Oct 2001) (WO 99/33980 (12/30/1997).

Claims 1-6 of U.S. Patent No. 6,297,367 teach an isolated polynucleotide of SEQ ID No.6 encoding a polypeptide of SEQ ID No. 1 which is 100% identical to instant SEQ ID No. 2 representing neutrokine-α, a member of the TNF superfamily of proteins (see sequence comparison A), thus anticipating instant claim 26. Disclosure of U.S. Patent No. 6,297,367 also shows methods of making fragments, derivatives, and variants with different degrees of identity to SEQ ID No.6 thus anticipating instant claims reciting portions of SEQ ID No. 2. U.S. Patent No. 6,297,367 also teaches fusion proteins comprising a first protein segment and a second protein segment fused together while the first protein segment comprises SEQ ID No. 1 (column 2, 2nd para; column 3, 2nd para) or a variant of SEQ ID NO. 1 thus anticipating instant claims of 90% or 95% variant polypeptides of SEQ ID NO. 2 with a second polypeptide as in claims 39, 78, 160, 178, 247, 268, 290, 307. Also taught are preparation of antibodies which specifically bind to selected regions of SEQ ID No. 1-5, 17 and 20 (column 2, 3rd para) thus anticipating 103, 160, 178, 213, 232, 290, 307, 341 reciting epitope-bearing regions of SEQ ID No.2. U.S. Patent No. 6,297,367 also discloses use of these polypeptides and polynucleotides to enhance or decrease TNF activities thereby providing therapeutic benefits, thus anticipating instant claims 196, 324 (column 3, 3rd para, lines 4 through end of para).

Conclusion

6. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday - Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
November 2nd, 2001

YVONNE EYLER, PH.D
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